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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/612,894	HAGBERG ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 21-29* is/are pending in the application.

4a) Of the above claim(s) *21-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18, and 21-29 are pending.
Claims 21-27 remain withdrawn as detailed in the previous Office Action of 11/15/2006.
Claims 1-18, 28, and 29 are examined on the merits

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/03/2008 has been entered.

This Office Action is in reply to Applicants' correspondence of 11/03/2008.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Withdrawn Claim Objections

1. The objection to claim 28, as set forth on page 2 of the Office Action of 05/01/2008, is **WITHDRAWN** in light of the amendment to claim 28.

New Claim Rejection - 35 USC § 101 Non-Statutory Subject Matter

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 1-18, and 21-29 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The rejected claims are drawn to a method of decreasing the level of t-PA antigen in a subject (claims 1-6) of preventing cardiovascular disease in a subject (claims 7-12), ameliorating cardiovascular disease in a subject (claims 13-18), and increasing t-PA activity in a subject (claims 28 and 29). The claimed inventions fall within an enumerated statutory category, namely a process.

The rejected claims are drawn to a methods identifying an allele or genotype, and advising a subject to engage in exercise.

In re Bilski No. 2007-1130 (Fed Cir. October 30, 2008) characterizes its machine-transformation test as "the governing test for determining patent eligibility of a process under section 101." Under this test, a process claim is patent-eligible if (and, as applied in Bilski, only if): "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." The claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing.

The rejected claims do not require the transformation of an article or physical object to a different state. For example, relevant to the rejected claims, one could identify the required allele or genotype by consulting a digital record in an electronic

database of nucleic acid sequence information, and one could advise a subject to engage in exercise using an algorithm that automatically generates a message based on the aforementioned identification. In the claims there is no requirement that allele or genotype is detected in nucleic acids from a sample, and there is no requirement that a subject in fact exercises and, for example, the level of t-PA antigen in the subject is reduced as a result of the exercise. Additionally, there is no result tied to the physical world. There is no required transformation of an article or physical object to a different state. Transformation of data is not considered a physical transformation.

As clearly noted in In re Comiskey No. 2006-1286 (Fed. Cir. Sept. 20, 2007), "the Supreme Court has reviewed process patents reciting algorithms or abstract concepts in claims directed to industrial processes. In that context, the Supreme Court has held that a claim reciting an algorithm or abstract idea can state statutory subject matter only if, as employed in the process, it is embodied in, operates on, transforms, or otherwise involves another class of statutory subject matter, i.e., a machine, manufacture, or composition of matter. 35 U.S.C. § 101." Regarding In re Comiskey, the USPTO noted, "[t]he Supreme Court has recognized only two instances in which such a method may qualify as a section 101 process: when the process 'either [1] was tied to a particular apparatus or [2] operated to change materials to a 'different state or thing.'" (quoting Flook, 2006-1286 17 437 U.S. at 588 n.9). In Diehr, the Supreme Court confirmed that a process claim reciting an algorithm could state statutory subject matter if it: (1) is tied to a machine or (2) creates or involves a composition of matter or manufacture. 450 U.S. at 184. There, in the context of a process claim for curing rubber that recited an

algorithm, the Court concluded that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." Id. (quoting Benson, 409 U.S. at 70);13 see also In re Schrader, 22 F.3d 290, 295 (Fed. Cir. 1994) (holding when a claim does not invoke a machine, "§ 101 requires some kind of transformation or reduction of subject matter").

Finally, the Comisky opinion states that mental processes- or processes of human thinking- standing alone are not patentable even if they have practical application. The Supreme Court has stated that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." Benson, 409 U.S. at 67. In Flook the patentee argued that his claims did not seek to patent an abstract idea (an algorithm) because they were limited to a practical application of that idea-updating "alarm limits" for catalytic chemical conversion of hydrocarbons. 437 U.S. at 586, 589-90. The Court rejected the notion that mere recitation of a practical application of an abstract idea makes it patentable, concluding that "[a] competent draftsman could attach some form of post-solution activity to almost any mathematical formula." Id. at 590.

In the case of the instantly rejected claims, there is no recitation of producing a real-word result that is tied to a machine or apparatus or causes a transformation of an article. In other words, the outcomes of the rejected methods lack a tie to the machine or apparatus and lack a physical transformation. Thus the claim is rejected as encompassing non-statutory subject matter.

The claims may be drawn to statutory subject matter if the methods are amended to specifically require the steps of, for example, obtaining a biological sample, and detecting particular nucleotide content in the sample, and having a subject perform a task such as moderate exercise training.

Withdrawn Claim Rejections - 35 USC § 112 1st ¶ - Written Description – New Matter

4. The rejection of claims 1-18, 28 and 29 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the inclusion of new matter, as set forth on pages 3-4 of the Office Action of 05/01/2008, is **WITHDRAWN** in light of applicants' arguments (p.6-7 of the Remarks of 11/03/2008), which are found to be persuasive. Applicants have argued that, with regard to the required limitations of the claims (i.e. advising) and the examples of the specification (i.e. engaging a subject in exercise), that 'in practice, the subject would be asked or advised to participate in an exercise regimen'.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement

This rejection is modified from the rejection as set forth on pages 4-11 of the Office Action of 05/01/2008. the instant rejection identifies a scope of the claimed invention that is enabled by the instant specification.

5. Claims 1-18, and 21-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (with regard to claim 1):

> A method of decreasing the level of tissue plasminogen activator (t-PA) antigen in a human subject, said method comprising:
> a) obtaining a biological sample from said subject, said biological sample comprising nucleic acids from said subject;
> b) detecting in said nucleic acids at least one 4G allele of the plasminogen activator inhibitor-1 (PAI-1) gene promoter; and
> c) engaging the human subject in moderate exercise training
> wherein the level of t-PA antigen in the human subject is decreased after said moderate exercise training.

and (with regard to claim 28):

> A method of increasing the level of t-PA activity in a human subject, said method comprising:
> a) obtaining a biological sample from said subject, said biological sample comprising nucleic acids from said subject;
> b) detecting in said nucleic acids a homozygous 4G allele geneotype of the plasminogen activator inhibitor-1 (PAI-1) gene promoter; and
> c) engaging the human subject in moderate exercise training
> wherein the level of t-PA activity in the human subject is increased after said moderate exercise training.

does not reasonably provide enablement for a method comprising advising a subject to engage in exercise training for a period of time sufficient to decrease the level of t-PA antigen (as required by claims 1-18) or increase the level of t-PA activity (as required by claims 28 and 29).

Nature of the Invention and Breadth of the Claims

The specification asserts that the instant invention relates to identifying genetic markers that correlate with improved success in increasing fibrinolysis levels in subjects through exercise training (paragraph [0003]) and provides an example in which several surrogate measures of fibrinolysis are provided (i.e.: PAI-1 activity; t-PA activity; and t-PA antigen). The claims are drawn to methods requiring advising a subject to engage in exercise training for a period of time sufficient to decrease the level of t-PA antigen

(claims 1-18) or increase the level of t-PA activity (claims 28 and 29), and encompass methods of preventing cardiovascular disease (claims 7-12) and ameliorating cardiovascular disease (claims 13-18 and 29).

The claims encompass subjects with at least one 4G allele (i.e. both homozygous 4G/4G subjects and heterozygous 4G/5G subjects) (claims 1, 4-7, 10-13, 16-20), subjects with heterozygous (i.e. 4G/5G) genotypes (claims 2, 8, and 14), and subjects with homozygous 4G/4G genotypes (claims 3, 9, and 15). The claims encompass exercise regimens comprised of extensive exercise (claims 4, 10, and 16), moderate exercise (claims 5, 11, and 17), and limited exercise (claims 6, 12, and 18).

The nature of the invention requires knowledge of a period of time of exercise training sufficient to decrease the level of t-PA antigen (where any such decreased level of t-PA may prevent or ameliorate cardiovascular disease) or increase t-PA activity.

Direction provided by the specification and working example

The specification teaches an example in which subjects were analyzed for several parameters indicative of fibrinolysis levels (i.e. PAI-1 and t-PA activities and t-PA antigen (paragraph [0031])) prior to participation in an exercise program to establish baseline values, and then after participation in an exercise program (paragraph [0045]).

The specification further teaches the genotyping of the PAI-1 gene promoter with respect to the 4G/5G polymorphic site (paragraph [0042]) by PCR amplification followed by restriction enzyme analysis of the resulting amplicon.

The instant specification provides an analysis of the changes in the measured parameters among the three possible (4G/4G; 4G/5G; 5G/5G) PAI-1 genotypes. The

specification indicates that the data provided is an analysis after moderate exercise training for six months (paragraphs [0047], [0048]). The data indicate the following results: the average PAI-1 activity decreased for the 4G/4G and 5G/5G groups, and increased for the 4G/5G group; the average t-PA activity increased for all groups; the average t-PA antigen decreased for all groups. The specification asserts that there is a tendency for subjects with 4G/4G genotypes to respond better than subjects with 4G/5G or 5G/5G genotypes (paragraph [0048]), the analysis of the data (P ANOVA) indicates that none of the changes are statistically significant.

The specification asserts that improving fibrinolysis prevented the development of cardiovascular disease or alleviated symptoms of cardiovascular disease (paragraph [0007]). There is no indication that either of these two qualities was actually measured in any of the analyzed subjects; Example 1 indicates that subjects were in fact excluded from the study if they had cardiovascular disease.

The specification presents results only from a population of human male and female subjects age 50-70.

The specification presents results only from participation in moderate exercise training (paragraph [0047], Table 1). The specification provides no results from subjects that participated in extensive exercise, or subjects that were involved only in limited exercise.

State of the art, level of skill in the art, and level of unpredictability

The level of skill in the art with regard to identification of PAI-1 gene promoter and t-PA genotypes is high, however the prior art and the instant specification shows

that the level of unpredictability in correlating any particular period of time of exercise training sufficient to decrease the level of t-PA antigen or increase t-PA activity is even higher.

Initially it is noted that the while the claims require being able to advise a subject with a 4G PAI-1 promoter allele to engage in exercise training 'for a period of time sufficient to decrease the level of t-PA antigen' or 'for a period of time sufficient to increase the level of t-PA activity', the specification does not give an indication of what such a time period may be for any individual. The analysis of parameters in the Examples provides only measurements at some endpoint that is not clearly identified in the specification, and thus does not provide a teaching of what 'period of time' is sufficient to have the required effects recite in the claims.

The extremely wide range of possible requirements for 'moderate exercise', as included in the results of the specification, adds to the unpredictability with regard to being able to advise a subject as to a period of time to exercise to have the required effect. This unpredictability is exemplified by the prior art of Womack et al (2000). Womack shows (Fig 1a) that after acute exercise, t-PA antigen does not remain increased as soon as 30 min post exercise (p.214 - Results in Abstract). Additionally, Cooper et al (2004) shows that both t-PA activity (Fig 1) and t-PA antigen decrease rapidly in the first 10 min after exercise (Fig 2). And while the Examiner recognizes that neither Womack et al nor Cooper et al stratify the results based on PAI-1 polymorphisms, the teachings of both references address the unpredictability of the

requirements of the claims in determining a period of time of exercise for any individual to have the effects required of the claims.

The unpredictability associated with the claimed methods further comes from the fact that the methods require 'advising' a subject to engage in some certain amount of exercise, but do not actually require the subject to perform any particular amount of exercise. It is wholly unpredictable if the mere act of 'advising' a subject to do something will result in the required effects of the claims.

The unpredictability of associating PAI-1 genotype with exercise-induced increases in fibrinolysis and the required effects such as preventing or ameliorating cardiovascular disease is further exemplified by Tiyasangthong (2001). Tiyasangthong examine the hypothesis that exercise training affects fibrinolytic variables (p.103), and that the changes in PAI-1 activity with exercise training is related to PAI-1 polymorphisms (p.107). The reference indicates that there are only significant changes in t-PA activity in heterozygous 4G/5G genotypes, and in t-PA antigen in the homozygous 4G/4G genotypes (Table 7).

Furthermore, claims drawn to methods for preventing cardiovascular disease may be considered as encompassing those methods which completely keep even the most minor forms of cardiovascular disease from occurring; wherein the pertinent method step is engaging a subject in exercise training. And while there may be an inverse relationship between physical activity and the risk of developing cardiovascular disease, the prior art of Sesso et al (2000) indicates that participation in physical exercise is not sufficient to provide a guaranteed prevention of any form or type of

cardiovascular disease (Table 2; p.976, right col., lns.44-53). Similarly, while measures of variables that are associated with the fibrinolytic system (i.e. t-PA activity and t-PA antigen concentration) are provided in the Examples of the specification, there is no indication that even the detected increase in t-PA activity shown in Table 1 is in fact sufficient to in any way ameliorate cardiovascular disease.

Quantity of experimentation required

There would be a large amount of experimentation required to make and use the invention in the full scope as claimed. One would have to conduct a large case-control randomized study to compare t-PA activity and concentration in individuals before any exercise and any point in time after any exercise period to determine what period of time is sufficient to decrease t-PA antigen or increase t-PA activity. Furthermore, one would have to establish that somehow the mere act of advising a subject to perform some particular amount of exercise is sufficient to have the effects required of the claims. There would be further experimentation required to determine if any such exercise in facts prevents cardiovascular disease or ameliorates disease. The fact that measures of t-PA activity and t-PA antigen are not necessarily indicative of those requirements is supported by the conclusions of Womack et al, which teaches, in regards to individuals whose t-PA increased with exercise, "further research is needed to better understand the mechanisms underlying the sustained enhanced fibrinolysis profile, and to determine whether exercise training improves fibrinolysis in this population". Such a study may or may not indicate that there is a reliable and statistically significant exercise dependent increase in prevention of cardiovascular

disease, or amelioration of cardiovascular disease, that is associated with a subject's PAI-1 genotype in any particular population.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the paucity of working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the invention claimed invention in the full scope of the claims..

Response to Remarks

Applicant has traversed the rejection of claims under 35 USC 112 1st¶ for lack of enablement (pages 9-10 of the Remarks). Applicants' arguments have been fully and carefully considered but are not found to be persuasive to fully withdrawn the rejection. It is noted that the rejection as set forth in this Office Action has identified scope that is enabled by the specification.

Applicants have cited Ex parte D'Antionio is support of a traversal that the data of the instant specification is not supported by the data of the cited Tyiasangthong thesis which presents the results of similar experimentation with regard to genotype analysis, exercise, and t-PA measurements. Initially it is noted that the BPAI decision cited by Applicants appears to be a non-precedential decision. That noted, the facts surrounding D'Antonio are different than the facts of the instant rejection. In the instant

rejection, there is enabled scope identified as that for which data is presented in the instant specification. Further, in the instant case, the issue is clearly set forth as an issue of lack of enablement for particular aspects of the claimed methods, not as a rejection for lack of utility.

Thus where Applicants have argued that the instant specification demonstrates statistically significant results (p.10 of Remarks), the Examiner maintains that there are in fact no results in the instant specification with regard to prevention of cardiovascular disease or amelioration of cardiovascular disease. Further, there is no indication that, as encompassed by the scope of the claims, advising a subject to engage in limited exercise will have the same effects on t-PA measurements as the moderate exercise provided in the specification.

The rejection as set forth is **MAINTAINED.**

Maintained Claim Rejections - 35 USC § 102

It is noted the claims of the instant application, rejected in this section of the Office Action as anticipated by the prior art, have been previously rejected in this Office action under 35 USC 112 1st ¶ as lacking enablement (i.e. a scope of enablement rejection). The prior art cited in this rejection teaches all of the steps of the claimed methods, and meets all of the limitations of the rejected claims. While the cited prior art anticipates an embodiment of the claims, it is does not enable the claims as addressed in the rejection of claims under 35 USC 112 1st ¶. Further it is noted that the specification of the instant application cannot be considered enabling for the methods of the prior art because the instant application does not present the same data, gathered from the same population, as the prior art.

6. Claims 1-18, 28, and 29 rejected under 35 U.S.C. 102(b) as being anticipated by Väisänen et al (1999) as cited in the IDS.

With regard to independent claims 1, 7, 13, and 28 Väisänen et al teaches methods comprising the steps of determining the genotype of a subject with respect to the 4G/5G PAI-1 gene promoter polymorphism (p.1118, left col., DNA analysis). The methods of Väisänen et al utilize the identification of subjects with 4G/4G, 4G/5G, and 5G/5G genotypes (Table 1), thus identifying subjects with at least one 4G allele as required by claims 1, 7, and 13, and subjects with two 4G alleles as required by claim 28. Further, the reference teaches engaging the subject in an exercise program (p.1118, left col., Cardiorespiratory fitness and exercise intervention), where the subjects of the scientific study are advised to perform a certain training program. With regard to the requirements that the exercise is of a period of time sufficient to decrease t-PA antigen (claims 1-18) or increase t-PA activity, The MPEP in chapter 2100 states:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

In the examination of the instant application, based on the teachings of the instant specification and the arguments of 02/05/2008 as presented by Applicants, the PTO has basis for believing that the exercise of Väisänen et al meets the limitations of the claims. Further, because the exercise of Väisänen et al is for the required period of time, the exercise prevents cardiovascular disease (claims 7-12) and ameliorates cardiovascular disease (claims 13-18 and 29). Where claims 13-18 and 29 require subject suffering

from cardiovascular disease, it is noted that the specification provides no limiting definition or guidance as to what is required for any individual to be 'suffering from cardiovascular disease'. As such, 'cardiovascular disease' is considered to be any amount of fibrin in the cardiovascular system, where the subjects of Väisänen et al would thus meet this interpretation of the term as in a population of individuals as taught by Väisänen et al at least some of the individuals would have some fibrin in their cardiovascular system.

Regarding claims 2, 3, 8, 9, 14, and 15, Väisänen et al teaches the analysis of subjects that were heterozygous (4G/5G) and homozygous for the 4G allele (4G/4G) at the promoter polymorphic site (p.1118, right col., lns.10-35), and that subjects from both of these groups responded to the exercise intervention (Table 1).

Regarding claims 4-6, 10-12, and 16-18, Väisänen et al teaches the particular nature of the exercise training with regards to duration of the regimen (p.1117, right col., Study design) and courses of exercise (p.1118, left col., Cardiorespiratory fitness and exercise intervention). The reference teaches that the study took place over three years, with exercise occurring three times a week for the first three months, followed by five times a week there after. This meets the definition of extensive exercise as defined in the specification (paragraph [0019]) as the exercise regimen of Väisänen et al includes at least 25 single courses of exercise, and takes place over about 400 days. Relevant to claims 6, 7, 11, 12, 17 and 18, because of the progressive nature of the definitions of limited and moderate exercise as defined in the instant specification

(paragraphs [0020]-[0021]), the exercise of Väisänen et al would necessarily be comprised of both limited and moderate exercise.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 102 as anticipated by the cited prior art. Applicants' remarks have been fully and carefully considered but are not found to be persuasive to withdraw the rejection. Applicants argue (p.11 of the Remarks) that Vaisanen does not teach 'advising a subject having at least on 4G allele at the PAI-1 gene to exercise to decrease t-PA antigen or increase t-PA activity'. However, the examiner maintains that Vaisanen does teach 'advising a subject to exercise', where, as Applicants have argued on p.7 of the Remarks regarding the previously set forth new matter rejection, when performing the actual task of having subject exercise 'in practice, the subject would be asked or advised to participate in an exercise regimen'. With regard to the argument that the advising to exercise is 'to decrease t-PA antigen or increase t-PA activity', this is merely and intended use of the 'advising', where according to the data of the instant specification, subjects with the required genotypes when they undergo moderate exercise training, the result is a decrease in t-PA antigen and an increase t-PA activity (e.g. according to the specification, regardless of PAI-1 genotype, when a subject exercises, the subject has an increase in t-PA activity). Thus the cited prior art meets these limitations.

The rejection as set forth is **MAINTAINED.**

Conclusion

7. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634